

This Week's Citation Classic

Flaherty J T, Reid P R, Kelly D T, Taylor D R, Weisfeldt M L & Pitt B.
Intravenous nitroglycerin in acute myocardial infarction. *Circulation* 51:132-9, 1975.
[Johns Hopkins University, School of Medicine, Baltimore, MD]

This paper describes the first use of intravenous nitroglycerin in patients with acute myocardial infarction. The acute hemodynamic effects were described in 12 patients with precordial ST segment monitoring demonstration improvement in regional ischemia as well. [The SCI[®] indicates that this paper has been cited in more than 360 publications.]

The Impact of Nitroglycerin

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In July 1972, when this work was begun, Friedberg's textbook of cardiology stated that nitroglycerin was not advised for patients with acute myocardial infarction. Despite this warning, we hypothesized that careful titration of an intravenous infusion would avoid the potentially deleterious side effects of hypotension and tachycardia frequently encountered when multiple sublingual tablets were given.

In this first paper, we described our experience in the Johns Hopkins Hospital Coronary Care Unit in the first 12 patients with acute myocardial infarction receiving nitroglycerin by intravenous infusion. Particularly humorous in retrospect was the need for us to prepare our own nitroglycerin for intravenous use. It was several years before we could convince the pharmaceutical industry of the potential financial reward for preparing a commercial product, thereby putting us out of the drug manufacturing business.

In this first study, we were primarily interested in demonstrating that the drug could be administered safely to such unstable patients. In addition to closely monitoring arterial pressure, we also measured left ventricular filling pressure by means of a thermodilution catheter placed in the pulmonary artery. We found that the first hemodynamic effect was a lowering of the pulmonary capillary wedge pressure without signif-

icant reduction in mean arterial pressure. In fact, in 3 of 12 patients, mean arterial pressure actually rose, presumably as a result of improvement in regional ischemia. We were also reassured by the favorable directional change in precordial ST segment voltages, indicating that despite lowering coronary perfusion pressure, the net effect of nitroglycerin was to improve the balance between myocardial oxygen supply and demand. In a subsequent larger study, we showed that lowering mean arterial pressure up to 20 percent still resulted in a beneficial effect on regional ischemia.¹ In addition, the subgroup of patients with the most severe degree of left-ventricular dysfunction obtained the greatest hemodynamic benefit, demonstrating not only a decrease in preload but, in addition, an increase in stroke volume. We later showed that a 48-hour infusion of intravenous nitroglycerin improved recovery of left ventricular function assessed 7-10 days later, presumably the result of salvage of ischemic myocardium.² Subsequently, the combination of intravenous nitroglycerin and intraaortic balloon pumping was shown to prevent ventricular remodeling in patients with extensive transmural infarction.³ More recently, a meta-analysis performed on seven published randomized placebo-controlled clinical trials, including our own, disclosed a 14 percent reduction in mortality ($P < .001$).⁴

Even with the advent of thrombolytic therapies, most cardiologists still utilize intravenous nitroglycerin with the hope of improving collateral flow to the distal ischemic bed until successful reperfusion can be obtained. For patients who are not candidates for thrombolytic therapy, intravenous nitroglycerin appears to provide benefit, as late as 14 hours after the onset of symptoms. Intravenous nitroglycerin has also been shown to be effective in the management of patients' unstable angina.⁵ Thus, almost 20 years after our first study, intravenous nitroglycerin remains the first line therapy, not only for acute myocardial infarction but also for unstable angina and acute pulmonary edema.

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2. Flaherty J T, Becker L C, Bulkley B H, Weiss J L, Gerstenblith G, Kallman C H, Silverman L K, Wei J, Pitt B & Weisfeldt M L. A randomized prospective trial of intravenous nitroglycerin in patients with acute myocardial infarction. *Circulation* 68:576-88, 1983.
3. Flaherty J T, Becker L C, Weiss J L, Brinker B H, Gerstenblith G, Kallman C H & Weisfeldt M L. Results of a randomized prospective trial of intraaortic balloon counterpulsation and intravenous nitroglycerin in patients with acute myocardial infarction. *J. Amer. Coll. Cardiol.* 6:434-46, 1985.
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